

# Characteristics and recent evolution of menopausal hormone therapy use in a cohort of Swedish women

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## **TITLE PAGE**

**Title:** Characteristics and recent evolution of menopausal hormone therapy use in a cohort of Swedish women

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## **ABSTRACT**

*Objectives* Menopausal hormone therapy (MHT) use is characterized by important geographical and temporal variations. Knowledge of these variations is necessary to interpret the results of epidemiological studies on MHT use and disease risk, and can contribute to understand national changes in diseases' incidence.

*Methods* We used data from a cohort study of women with information on lifetime MHT use collected in 2003-2004 to describe the characteristics and recent evolution of MHT consumption in Sweden.

*Results* Among the 17,450 postmenopausal participants, prevalence of use declined by approximately 30% between 2001 and 2003. MHT was almost no longer used to prevent osteoporosis, and worry about side effects was often cited as a reason for stopping treatment. MHT mostly consisted in estradiol used alone or opposed with either norethisterone acetate or medroxyprogesterone acetate, or in low-potency estrogens. An estimated 30% of participants initiated MHT before menopause. The cumulative monthly dose of progestagen was generally doubled in continuous-combined compared with sequential combinations.

*Conclusions* In this cohort, both prevalence of use and reasons for initiating MHT have varied between 2001 and 2003, while the modalities of use remained essentially the same.

## INTRODUCTION

The publication in July 2002 of the first results of the Women's Health Initiative randomized controlled trial <sup>1</sup> brought about a dramatic change in the use of menopausal hormone therapy (MHT) in numerous countries, probably extended with the publication, in August 2003, of the observational Million Women Study results.<sup>2</sup> In December 2003, in view of these data which raised important safety concerns for MHT use regarding breast cancer and cardiovascular diseases, the European Medicines Agency restricted indications for MHT to the treatment of menopausal symptoms – it should no longer be considered as first line treatment for prevention of osteoporosis – and recommended to limit duration of use and doses.<sup>3</sup> From 2002-2003, a marked decrease in the prevalence of MHT use has been observed in several countries; in the United-States <sup>4-8</sup> as in some other countries,<sup>9-11</sup> this was paralleled with a decrease in breast cancer incidence, which can however not be firmly attributed to the drop in MHT use.<sup>12</sup>

MHT, as the most effective treatment to alleviate menopausal symptoms,<sup>13</sup> is still often used, and several issues regarding its health risk/benefit ratio remain unresolved. Of them is whether different modalities of use bear different risks. Regarding breast cancer, epidemiologic evidence suggests that this may be the case. For example, in a French cohort study, it was found that combined MHT containing progesterone or dydrogesterone were associated with a lower breast cancer risk than MHT containing other progestagens;<sup>14</sup> a German case-control study found differences between continuous combined and sequential therapies as well as between different types of progestagens, but suggested that the effective progestagenic dose was in fact driving these differences in risk.<sup>15</sup>

In Scandinavian countries, the associations observed between estrogen-progestagen use and breast cancer risk have been generally particularly marked.<sup>16</sup> One should seek the reasons for this observation. This implies at least knowing in details the characteristics of MHT use in these countries, in order to contrast them with those in other countries.

Moreover, to date, relatively little information has been available on the recent evolution of MHT use in Scandinavian countries. Such knowledge may be very useful to interpret possible changes in the national incidence of breast cancer (or other diseases).

Using data from a large cohort study of Swedish women with information on lifetime MHT use collected in 2003-2004, we therefore aimed at describing and compare MHT use in Sweden before and after the publication of the Women's Health Initiative results. We also aimed at characterizing the modalities of MHT use in this country.

## **METHODS**

### **The Women's Lifestyle and Health Cohort Study**

As described previously,<sup>17</sup> the Swedish component of the Women's Lifestyle and Health study was initiated during 1991–1992, when a population-based sample of 96,000 women born between 1943 and 1962 and residing in the Uppsala Health Care Region was invited to answer a self-administered questionnaire. Requested information concerned oral contraceptives use, dietary habits, reproductive history and other lifestyle factors. Of the invited women, 49,259 completed the questionnaire. A follow-up study was initiated in 2003-2004 among the 47,859 responders who were still alive and living in Sweden in October 2002.<sup>18</sup> Questions were mostly updates on exposure information from the 1991-1992 questionnaire. A total of 34,403 women completed the follow-up questionnaire, between February 2003 and January 2004 (half of them before the end of June 2003).

The Swedish Data Inspection Board and the regional Ethical Committee approved the study.

### **Assessment of menopausal status; population for analysis**

The present study describes MHT use among postmenopausal women. Menopausal status was assessed using the following information, derived from the 2003-2004 questionnaire: current menstrual status (menstruation stopped / menstruation currently irregular / natural menstruation currently regular / menstruation due to ongoing hormonal medication), reason for menstruation cessation (natural reasons / removal of ovaries /

removal of uterus / use of an intrauterine device (IUD) / pregnancy / stop of hormonal treatment / other reason), age when menstruation stopped, and age at completion of the questionnaire.

At the time of completion of the 2003-2004 questionnaire, women were considered premenopausal if they had regular natural menstruation, or if their menstruation was currently irregular, or if they were pregnant (n = 13,542); naturally postmenopausal if their menstruation had stopped for natural reasons or when hormonal treatment ceased (n = 12,310); surgically postmenopausal if their menstruation had stopped because of removal of ovaries (n = 910); and postmenopausal for other reasons if their menstruation had stopped for other reasons except use of an IUD or removal of uterus (n = 1,733). For the remaining women (menstrual status unknown, n = 640; menstruation stopped because of hysterectomy, n = 2,299; women still menstruating because of ongoing hormonal medication, n = 2,104; women using an IUD, n = 865), those aged 53 years old or more at the time of completion of the 2003-2004 questionnaire were considered postmenopausal (n = 2,497). This age cut-off was chosen because among naturally postmenopausal women with a known age at menopause, 75% were already postmenopausal at that age.

Finally, 17,450 women were considered postmenopausal at the date of completion of the 2003-2004 questionnaire and therefore included in the present study. Age at menopause was unknown for 3,847 of them (including those 934 whose menstruation stopped when hormonal treatment ceased).

At other dates, women were considered as postmenopausal if i) they had a known age at menopause and had already reached menopause at the date considered, or ii)

they were postmenopausal in 2003-2004 with an unknown age at menopause but were aged more than 53 years at the considered date, or iii) they had an unknown menopausal status in 2003-2004 but were aged more than 53 years at the date considered.

### **Assessment of MHT use**

Information on lifetime MHT use was mostly derived from the 2003-2004 questionnaire, through a specific section where women were requested to report any episode of use of an hormonal treatment containing i) estrogens in forms of pills, patches, or vaginal pills, creams or rings, and/or ii) progestagens in forms of pills or IUD. This section of the questionnaire excluded hormonal contraceptives use, which was specifically assessed in another section.

Women were first asked if they had ever used a treatment as described above and then to detail up to four episodes of use. For each episode, they should specify the dates of start and of end of use, the brand name of the estrogen or combined estrogen-progestagen preparation, and/or the brand name of the progestagen preparation together with the number of days per month it was used. To facilitate recall, the questionnaire was accompanied with a color brochure with names and photographs of almost all estrogenic or estrogen-progestagen preparations as well as oral progestagens sold in Sweden since 1980.

Data derived from the 1991-1992 questionnaire was further used to identify supplementary episodes of MHT not reported in the 2003-2004 questionnaire. This questionnaire indeed requested summary information of MHT use among women who



had already reached menopause, i.e. ever having used such a treatment, age at first use and total duration of use.

Estrogens were classified as low-potency estrogens if they consisted of estriol (either orally or vaginally administered) or in vaginally administered estradiol or dienestrol. Otherwise, they were classified as medium-potency estrogens. Tibolone, a synthetic steroid structurally related to norethynodrel which possesses estrogenic, progestational and androgenic properties, was considered as MHT. Estrogen-progestagen combinations were further classified according to the number of days progestagen was provided per cycle, as continuous if the progestagen was used more than 21 days (mostly 28 days) per cycle, and as sequential (mostly 10, 12 or 14 days) otherwise.

### **Statistical methods**

All the statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC). Prevalence of MHT use at a given time point was calculated as the number of women who were (currently) using MHT at that time divided by the number of women who were postmenopausal at that time, multiplied by 100. Current MHT use at a given date (month/year) was defined as an MHT being in use at the start of the considered month.

## RESULTS

Table 1 shows the main characteristics of the study population in 2003-2004. Among the 17,450 women who were classified as postmenopausal, the mean age was 55.7 years (SD, 4.0) and the mean age at menopause was 49.1 years (SD, 5.1). Most women had ever used hormonal contraceptives. Almost half of the women (47.4%) were overweight or obese. Finally, the large majority of women were non-smokers (Table 1).

In total, 9,632 women (55.2%) reported ever-use of MHT. The overall prevalence of use (i.e. the percentage of current users) was 38.9% in August 2001 and 29.3% in December 2003, among women who were classified postmenopausal at these dates (Table 2). This decrease was seen in all age categories. Specifically, among women 50-55 and 55-60 years old, a decrease of 26-27% was observed between August 2001 and December 2003. The drop in MHT use seemed restricted to MHT containing medium-potency estrogens (Table 2).

The reasons for starting MHT are shown in Table 3 among women who were postmenopausal when initiating treatment in August 2000-August 2001, and in August 2002-December 2003. Most women gave hot flushes/sweating and/or vaginal dryness as contributing reasons for starting MHT use. Troubles with sleeping was also often cited, as the influence of doctor. Hot flushes/sweating and prevention of osteoporosis were less often cited as contributors to starting MHT in August 2002-December 2003 than in August 2000-August 2001. No other marked difference between the two periods was seen.

There was no substantial change in reasons given for stopping MHT (among participants who were postmenopausal at the time of treatment stop) between August

2000-August 2001 and August 2002-December 2003 (Table 4). The reasons most often cited by women were that they felt that the treatment was not needed anymore, or that they worried about side effects.

Table 5 shows the distribution of the types of MHT used, globally (that is, whenever used), as well as in August 2001 and December 2003 among postmenopausal women. Overall (Table 5) or in different age categories (data not tabulated), there was no substantial variation between August 2001 and December 2003 in the distribution of MHT used. Globally, the most frequently reported episodes of MHT consisted in oral combinations of estradiol and norethisterone acetate (NETA), either continuous (20.1%) or sequential (13.3%), followed with unopposed estradiol, either in form of patches (6.8%) or pills (5.5%), low-potency estrogens (11.4%), and oral combinations of estradiol and sequential medroxyprogesterone acetate (MPA) (7.1%). However, in 2001 as in 2003, the proportion of continuous versus sequential MHT was higher (Table 5). When opposed with a progestagen, medium-potency estrogens consisted mainly in oral estradiol. By contrast, when used alone, they often consisted in patches of estradiol, closely followed with oral estradiol (Table 5).

The mean cumulative monthly dose of MPA used in oral continuous combinations was 140 mg, and 279 mg in oral sequential combinations. The mean cumulative monthly dose of NETA used in oral continuous combinations was 24.2 mg, and 12.6 mg in oral sequential combinations (data not tabulated).

Finally, the mean age at MHT start was 48.3 years old (SD, 5.1). The first use of MHT containing medium-potency estrogens (or Tibolone) occurred at a mean age of 48.7 (SD, 4.5) years old. The mean age at first use of sequential MHT was 48.4 (SD,

4.2) years old, whereas it was 50.8 (SD, 4.3) years old for continuous MHT. Of the participants with a known age at menopause who ever used MHT containing medium-potency estrogens (or Tibolone), 30.4% began its use before onset of menopause (data not tabulated).

## DISCUSSION

In this large sample of postmenopausal Swedish women, we observed a drop of approximately 30% in the prevalence of MHT use between August 2001 (before the release of the first results of the Women's Health Initiative trial) and December 2003 (after their release as well as those of the Million Women Study). MHT was almost no longer used to prevent osteoporosis, and worry about side effects was often cited as a reason for stopping treatment. There were no marked changes in the types of MHT used, which mostly consisted in oral estradiol opposed with either NETA or MPA (more often continuously than sequentially), estradiol used alone, or low-potency estrogens. The present study also illustrates some complexities of MHT use in Sweden. First, MHT is relatively often initiated some years before onset of menopause. Second, sequential estrogen-progestagen combinations are given to younger women than are continuous combinations. Third, estradiol is often given in form of patches when used alone, but more rarely when opposed with a progestagen. And fourth, the cumulative monthly dose of progestagen is generally doubled in continuous estrogen-progestagen MHT compared with sequential combinations.

Our observation of sequential estrogen-progestagen MHT given to younger women than continuous-combined regimens is corroborated by a recent survey among Swedish gynecologists, which indicated that 91% of them recommended that perimenopausal women with their last menstruation within two years were treated with estrogens in combination with sequentially administered progestagens, and that 85% recommended continuous-combined MHT later.<sup>19</sup>

In our study, we found the overall prevalence of MHT use to be 38.9% among postmenopausal women (and 43.9% among women aged 55 to 60 years old) in 2001, before the release of the Women's Health Initiative results. This is concordant with other Swedish data. One study reported a prevalence of 46% among women 54 years of age resident in the city of Göteborg, in 1998.<sup>20</sup> In 2000-2001, 35% of women 55 years old from two primary health-care districts covering a rural part of Sweden were using MHT.<sup>21</sup> Finally, in another study performed among women 50-64 years old living in the Lund area of southern Sweden, 39% of participants were current users of MHT when answering a questionnaire between 1996 and 2000.<sup>22</sup>

The magnitude of the decrease in MHT prevalence we observed in our study (approximately 30%) is consistent with trends from other studies over comparable periods. Indeed, it was found that the prevalence of use in two primary health-care districts covering a rural part of Sweden dropped from 24% in 2000-2001 to 16% in 2002-2003 (i.e., a 33% drop).<sup>21</sup> This was however slightly less marked than in the United-States, where prescriptions fell by 40% between 2001 and July 2003.<sup>23</sup>

Reasons for starting or stopping MHT did not change markedly between 2000-2001 and 2002-2003. Almost all women cited treatment of at least one of the listed menopausal symptoms as having contributed to the initiation of MHT. Heart disease was rarely cited as a contributor to MHT start, in 2000-2001 as well as in 2002-2003. The likely explanation is that strong doubts regarding a protective effect of MHT on coronary heart disease emerged from 1998, when the Heart and Estrogen/progestin Replacement Study could not find the expected secondary preventive effects of MHT.<sup>24</sup> We also found that prevention of osteoporosis became less often a reason for starting MHT, although

its ability to increase bone mineral density was known for long and its ability to reduce the risk of fracture was demonstrated with the Women's Health Initiative trial.<sup>1</sup> There exist other treatments that are efficient to prevent osteoporosis, such as bisphosphonates, which are becoming easier to use and increasingly popular.<sup>25</sup> As a likely consequence, in a study performed among Swedish gynecologists, 25% in 2003 stated that risk factors for osteoporosis were absolute indications for MHT, versus 60% in 1996.<sup>19</sup> Worry about side effects was a frequently cited reason for stopping in 2003 but also just before 2002. This is likely explained by the fact that the results of studies suggesting an increased risk of breast cancer with MHT use have been publicized since 1997, with the release of an important meta-analysis.<sup>26</sup> As a result, in a study performed among women living in the city of Göteborg, in 1998, two-thirds of the women thought that the risk of breast cancer increased due to MHT use.<sup>20</sup> From that time on, growing evidence has accumulated, showing an increase in breast cancer risk associated with the use of MHT, especially estrogen-progestagen combinations.<sup>27</sup>

One of the limitations of our study is that data on MHT use were self-reported, and thus affected by recall bias, causing under-estimation of prevalence of use if some women forgot to mention MHT use, as well as errors in dates of treatment initiation, in treatment durations, or in brand names. However, this bias should have only marginally affected our results since the time points we focused on (August 2001 and December 2003) are close to the time when information was collected (February 2003 to January 2004). Indeed, good agreement between prescription data and self-reported use of MHT are generally found, especially for recent use.<sup>28;29</sup> Furthermore, to aid memory, the questionnaire was accompanied with a color brochure with names and photographs of

almost all MHT sold in Sweden since 1980. Another limitation is that women could report, in the section of the 2003-2004 questionnaire dedicated to MHT, use of progestagens (without estrogens) to for instance prevent disturbances in the bleedings or ovarian cysts. However, we restricted our population for analysis to postmenopausal women, in order to catch more specifically hormonal treatments used for purposes linked to menopause. Finally, one should stress that our description of MHT use applies to a specific population (women who accepted to participate in an epidemiological study), in a given region (the Uppsala Health Care Region, Sweden) and during a specific period of time (around year 2002). However, if prevalences of use we observed may not be applicable to the entire postmenopausal Swedish population, time trends as well as characteristics of the treatments used are more likely to reflect prescription habits at a national level.

In conclusion, in this cohort of Swedish women, both prevalence of use and reasons for initiating MHT have varied between 2001 and 2003. The present study also illustrates some specificities of MHT use in Sweden, which should be borne in mind when interpreting the results of epidemiological work on the relation between MHT use and the risk of disease. Detailed assessment of MHT use, as was done in the Women's Lifestyle and Health cohort, should be encouraged so that epidemiological studies will be able to disentangle the effects on the risk of diseases (such as breast cancer) of various treatment parameters, such as molecule, dosage, and timing of initiation.



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### *Conflict of interest*

Authors declare no commercial associations that might pose a conflict of interest in connection with the submitted manuscript.

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Table 1. Main Characteristics of the 17,450 Postmenopausal Women, Women's Lifestyle and Health Study, Sweden, 2003-2004.

	N (%) or mean (SD)
<b>Age, years</b>	
< 45	355 (2.0%)
[45-50[	1,139 (6.5%)
[50-55[	5,072 (29.1%)
[55-60[	8,757 (50.2%)
≥ 60	2,127 (12.2%)
Mean (SD)	55.7 (4.0)
<b>Type of menopause</b>	
Natural	12,310 (70.5%)
Surgical	910 (5.2%)
Other	1,733 (9.9%)
Age cut-off criteria*	2,497 (14.3%)
<b>Age at menopause, years†</b>	
All types of menopause	49.1 (5.1)
Natural menopause	50.2 (3.9)
Surgical menopause	44.6 (7.2)
Other type of menopause	44.2 (7.0)
<b>Ever-use of hormonal contraceptives</b>	
Yes	14,183 (81.5%)
No	3,215 (18.5%)
Missing	52 (0.3%)
<b>Body mass index, kg/m<sup>2</sup></b>	

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≤ 20	742 (4.3%)
[20-25[	8,210 (47.0%)
[25-30[	6,034 (34.6%)
≥ 30	2,227 (12.8%)
Missing	237 (1.4%)
Mean (SD)	25.6 (4.3)

**Smoking status**

Never smoked regularly	7,836 (44.9%)
Current regular smoker	3,611 (20.7%)
Past regular smoker	5,748 (32.9%)
Ever smoked regularly (recency not specified)	172 (1.0%)
Missing	83 (0.5%)

**Education, years**

< 9	2,295 (13.2%)
10–12	8,003 (45.9%)
13–15	4,122 (23.6%)
≥ 16	2,602 (14.9%)
Missing	428 (2.5%)

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\* Women with an unknown menopausal status but aged 53 or more years old.

† Among women with a known age at menopause.

Table 2. Prevalence of MHT Use Among Postmenopausal Women at Different Time-points, Women's Lifestyle and Health Study, Sweden, 2003-2004.

	August 2001		December 2003	
	Number of postmenopausal women*	Percent current users among postmenopausal women	Number of postmenopausal women*	Percent current users among postmenopausal women
<b>Any type of MHT</b>				
Overall	12,999	38.9%	7,459	29.3%
< 45 years old	406	18.0%	92	10.9%
[45-50[ years old	1,061	25.2%	414	22.9%
[50-55[ years old	4,758	36.7%	1,960	27.1%
[55-60[ years old	6,774	43.9%	3,767	32.0%
≥ 60 years old	0	-	1,226	28.3%
<b>Specific types of MHT</b>				
Medium-potency†	12,999	28.0%	7,459	19.6%



Estrogens alone	12,999	7.2%	7,459	5.2%
Estrogen- progestagen	12,999	20.2%	7,459	14.2%
Unspecified	12,999	0.6%	7,459	0.3%
Low-potency estrogens	12,999	3.2%	7,459	3.4%
Progestagens alone	12,999	0.6%	7,459	0.5%
Not specified	12,999	7.1%	7,459	5.8%

\* excluding ever users with an unknown recency of use (944 in August 2001; 566 in December 2003).

† MHT containing medium-potency estrogens, or Tibolone (classified as estrogen-progestagen MHT).

Table 3. Reasons for Starting\* MHT During Different Periods of Time, Women's Lifestyle and Health Study, Sweden, 2003-2004.

	Between August 2000 and August 2001 (n† = 205)	Between August 2002 and December 2003 (n† = 303)
<b>Treatment of menopausal symptoms</b>		
Hot flushes, sweating	60.5%	50.8%
Psychological problems	10.2%	11.2%
Trouble sleeping	33.7%	28.7%
Vaginal dryness	40.5%	45.5%
Urinary infections	12.7%	10.2%
Problems with bleeding	7.3%	10.2%
Premenstrual trouble	1.5%	5.6%
<i>Any of these reasons</i>	<i>92.2%</i>	<i>95.0%</i>
<b>Prevention of disease</b>		
Osteoporosis	11.7%	4.6%
Heart disease	2.9%	1.3%
<b>Other reason</b>		
My doctor thought I should take it	22.0%	19.8%

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I wanted to feel “younger”	2.0%	2.0%
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\* Each participant could choose several reasons in the list provided. Totals are therefore >100%.

† Excluding women who did not give any reason for starting (n = 2 among those who started between August 2000 and August 2001; n = 5 among those who started between August 2002 and December 2003).

Table 4. Reasons for Stopping\* MHT During Different Periods of Time, Women's Lifestyle and Health Study, Sweden, 2003-2004.

	Between August 2000 and August 2001 (n† = 211)	Between August 2002 and December 2003 (n† = 1,032)
<hr/> The medication caused trouble or adverse effects		
Weight gain	14.2%	11.5%
Bleedings	4.7%	7.0%
Sore breasts	4.7%	6.2%
Other troubles	10.0%	9.6%
<i>Any of these reasons</i>	26.5%	27.8%
I stopped taking hormonal medicine when I got disease‡	11.4%	11.2%
I felt I did not need it anymore	52.6%	44.9%
My doctor suggested I should stop	16.6%	21.4%
I worried about adverse side effects	42.7%	41.5%

\* Each participant could choose several reasons in the list provided. Totals are therefore >100%.

† Excluding women who did not give any reason for stopping (n = 15 among those who stopped between August 2000 and August 2001; n = 41 among those who stopped between August 2002 and December 2003).

‡ High blood pressure, diabetes, angina of the heart, coronary infarction, uterine cancer, ovarian cancer, breast cancer, other disease.

Table 5. Main Types of MHT Used, Globally and at Different Time Points, Women's Lifestyle and Health study, Sweden, 2003-2004.

	All episodes (n* = 11,281)	MHT currently in use in August 2001 (n* = 4,088)	MHT currently in use in December 2003 (n* = 1,747)
<b>Opposed Estrogens</b>			
Oral Estradiol + NETA, continuous	20.1%	25.3%	24.2%
Oral Estradiol + NETA, sequential	13.3%	7.6%	7.5%
Oral Estradiol + MPA, sequential	7.1%	4.9%	1.8%
Combined patch†	4.7%	3.8%	3.5%
Oral CEE + MPA, continuous	4.4%	7.5%	5.8%
Oral Estradiol + MPA, continuous	4.0%	4.2%	7.5%
Estrogens opposed with an hormonal IUD	0.9%	1.3%	1.5%
Other‡ / Type not specified	8.1%	6.1%	5.0%
<b>Medium-potency estrogens used alone</b>			
Patch of Estradiol	6.8%	8.0%	7.0%
Oral Estradiol	5.5%	8.3%	9.2%

Oral CEE	3.3%	5.1%	4.8%
Type not specified	1.6%	1.9%	1.7%
<b>Low-potency estrogens</b>	11.4%	10.2%	14.4%
<b>Tibolone</b>	2.9%	3.7%	3.8%
<b>Progestagens used alone</b>	5.8%	2.0%	2.2%
<b>Total</b>	100%	100%	100%

Abbreviations: CEE, conjugated equine estrogens; IUD, intra-uterine device; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate.

\* Excluding episodes without any information on type (n = 3,516 of all episodes; 971 of current episodes in August 2001; and 442 in December 2003).

† Patch containing both estradiol and NETA (sequential or continuous).

‡ This category includes oral CEE + MPA used sequentially; oral CEE + NETA; oral combinations of estradiol + levonorgestrel; and patches of estrogens associated with an oral progestagen, which were all only marginally used.

